REMARKS

I. Status Summary

Claims 1, 5-12, 14-18, and 20-46 are pending in the subject application and have been examined by the U.S. Patent and Trademark Office (hereinafter "the Patent Office").

Claims 1, 5-12, 14-16, 26-28, and 42 have been rejected under 35 U.S.C. 112, second paragraph, upon the contention that they are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5-11, 16, 26-28, 42, and 46 have been rejected under 35 U.S.C. 112, first paragraph, upon the contention that the specification, while being enabling for mutants of bovine gamma-crystallin of SEQ ID NO:22 obtained by mutations at positions identified in claim 12, does not reasonably provide enablement for mutants of other crystallins, much less for other proteins with mutations at beta sheet structure as claimed.

Claims 1, 5-11, 16, 26-28, 42, and 46 have been rejected under 35 U.S.C. 112, first paragraph, upon the contention that they contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 12 and 15 have been objected to as being dependent from a rejected base claim.

Claims 1-4, 8, 13, 17-25, 29-41, and 43-46 have been canceled without prejudice. Applicants respectfully reserve the right to file one or more continuation and/or divisional applications with claims directed to the subject matter encompassed by one or more of canceled claims 1-4, 8, 13, 17-25, 29-41, and 43-46.

Claims 5-7, 9-12, 14-16, 26-28, and 42 have been amended. The amendments to claims 5-7, 9-12, 14-16, 27, and 28 are formal in nature, and are limited to updating the dependency of these claims from claim 1 to claim 42 and/or harmonizing the preambles to reflect the preamble of claim 42. Additional

support can be found in the original claims as filed, including particularly claims 1 and 8. Support for the amendments to claim 42 can be found throughout the specification as filed, including particularly at page 4, last full paragraph. Additional support can be found at page 5, lines 1-4, in the third full paragraph on page 13, and in Figure 11. Thus, no new matter has been added by the amendments to the claims.

New claim 47 has been added. Support for new claim 47 can be found in the original claims, including particularly original claims 1 and 8. Additional support can be found in the Example beginning on page 16 and continuing through page 24, in which the method for producing the mutagenized gamma-crystallin polypeptides of the presently disclosed subject matter is described. Thus, no new matter has been added to the application as a result of the addition of new claim 47.

Reconsideration of the subject U.S. patent application based on the amendments and remarks presented herein is respectfully requested.

II. Response to the 35 U.S.C. §112, Second Paragraph, Rejection

Claims 1, 5-12, 14-16, 26-28, and 42 have been rejected under 35 U.S.C. 112, second paragraph, upon the contention that the claims are indefinite. According to the Patent Office, claims 1 and 42 include a narrower range within a broader embodiment within the same claim. Additionally, the Patent Office asserts that with respect to claims 1, 42, and 44, the term "antibody-like binding activity" is not clear and the claims use two different terms with respect to "antibody-like", "binding activity", and "binding specificity".

After careful review of the rejection and the Patent Office's bases thereof, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that claims 1, 8, and 44 have been canceled without prejudice, and thus the instant rejection is believed to be moot as to these claims.

Turning now to the assertion that claim 42 recites a broad range with a narrow range that falls within the broad range thus rendering the claim indefinite,

applicants respectfully submit that claim 42 has been amended to remove the recitation of "at least two" β-strands. As such, and without acquiescing to the Patent Office's assertion that the claim as previously presented was indefinite, applicants respectfully submit that the instant basis for the rejection under 35 U.S.C. § 112, second paragraph, has been addressed. Applicants respectfully request that it be withdrawn at this time.

Turning now to the assertion that the recitation of "antibody-like binding activity" renders claim 42 indefinite, applicants respectfully submit that the phrase "antibody-like" has been removed from the claims, which now recite *inter alia* mutagenized gamma-crystallins with a new binding activity towards a binding partner. Applicants respectfully submit that this amendment addresses the instant basis upon which the rejection of claim 42 under 35 U.S.C. § 112, second paragraph, is based.

Accordingly, applicants respectfully submit that claim 42 is believed to be in compliance with 35 U.S.C. §112, second paragraph. Claims 5-7, 9-12, 15, 16, and 26-28 have all been amended to depend directly or indirectly from claim 42, and thus it is believed that the amendments to claim 42 also address the instant rejection as applied to claims 5-7, 9-12, 15, 16, and 26-28. As such, applicants respectfully request that the rejection of claims 5-7, 12, 14-16, 26-28, and 42 under 35 U.S.C. 112, second paragraph, be withdrawn at this time. Allowance of these claims is respectfully and earnestly solicited.

III. Response to the Enablement Rejection

Claims 1, 5-11, 16, 26-28, 42, and 46 have been rejected under 35 U.S.C. 112, first paragraph, upon the contention that while the specification enables the mutants of bovine gamma-crystallin of SEQ ID NO. 22 obtained by mutations at positions identified in claim 12, it does not reasonably provide enablement for mutants of crystallins other than bovine γ-crystallin, and also does not enable other proteins with mutations at beta sheet structure as claimed.

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that claims 1, 8, and 46 have been canceled without prejudice, and thus the instant rejection is believed to be moot as to these claims. Furthermore, the subject matter of the remaining claims relates to mutagenized gamma-crystallins, and thus the Patent Office's assertions with respect to other proteins with beta sheet structure have also been rendered moot.

In support of the instant rejection, the Patent Office asserts that no working examples are provided for any other mutants of crystallins than those shown in the examples, such that an undue amount of experimentation would be required for an expert in order to develop a new protein having a new or improved antigen binding activity towards a binding partner.

Applicants respectfully disagree. Firstly, applicants respectfully note that the specification provides substantial guidance as to locations of the mutations. For example, mutations can be located in two, three, or four beta-strands of at least one beta-sheet of a gamma-crystallin (*see* page 9, first and third full paragraphs of the instant specification). Gamma-crystallins have been highly conserved during evolution. Mature bovine gamma-crystallin, for example, includes 174 amino acids (not including the initiator methionine), of which forty (40) amino acids are located in the outer beta sheets (N- and C-terminal domains). Twenty (20) residues are located in the N-terminal domain and 20 residues are located in the C-terminal domain. Out of these residues, 12 amino acids of the N-terminus are located on the surface and 13 amino acids of the C-terminus are located on the surface. To summarize, 25 amino acids out of the total 174 amino acids are located on a surface of a beta strand. Thus, only 14% of the total amino acids of gamma-crystallin are candidates for mutation in the presently disclosed subject matter.

Considering the size of a gamma-crystallin on the one hand and the number of amino acid residues located on a surface of a beta-strand on the other

hand, applicants respectfully submit that there are only a small number of amino acids to be considered as candidates for mutation by one of ordinary skill in the art. Additionally, the mutated amino acids are located in two, three, or four beta-strands, which further reduces the number of alternatives available.

Applicants respectfully submit that an element of the presently claimed mutated proteins is the location of the mutations within amino acids located on a surface and also found in two, three, or four beta-strands. As noted above, only 25 amino acids in a gamma-crystallin fulfill these conditions. The mutations within these 25 amino acids can be chosen arbitrarily or by site-specific mutagenesis. A person of ordinary skill in the art would not have to know from the outset precisely which amino acid or acids need to be changed (*see* page 7, third paragraph of the instant specification). A random mutagenesis system would be understood by one of ordinary skill in the art to provide a large number of modified proteins, but even several billion mutants can be simply managed and screened through methods well known in the art and fully described in the instant specification (*see* pages 11-12).

Applicants further respectfully submit that the phage display methods and bacterial expression systems described (*see* page 11 of the instant specification, No. 1 and No. 2) are only two examples out of several known in the art. The examples of the instant specification also sufficiently detail management of mutant libraries (No. 4, last line of page 11-page 12). Screening such libraries for binding specificity to a selected binding partner would pose no problem to one skilled in the art. Again, of primary importance is the introduction of mutations at amino acids in two, three, or four beta-strands located on a surface of the protein. As these mutations are performed within only 25 different amino acids, a random mutagenesis system can directly guide a skilled artisan to the claimed protein (page 7, third paragraph, and page 9, last two paragraphs, of the instant specification).

Keeping in mind the options of random or site-directed mutagenesis, the potentially large variety of mutated proteins so obtained can be easily screened in a second step. This is accomplished by placing the mutated proteins in

contact with a chosen binding partner. Applicants respectfully submit that the binding partner will "automatically" find a corresponding mutated protein in a targeted manner, and that this can be accomplished by one of ordinary skill in the art with only routine experimentation after review of the instant specification.

Additionally, applicants respectfully submit that the Beste *et al.* reference cited by the Patent Office does not support the instant rejection. According to the Patent Office, Beste *et al.* discloses "a similar method of creating mutant antibody-like proteins derived from lipcalin". (Official Action at page 6). Applicants respectfully note, however, that the method of Beste *et al.* is not similar to the instantly disclosed methods. Rather, the method disclosed therein is different in that "those parts of the lipocalin molecule are mutated which connect beta sheets." (*see* Beste *et al.* at page 1898) These peptide loops being mutated are outside of the beta sheets, connecting two neighboring beta sheets. Contrary thereto, the presently disclosed subject matter relates to a different approach in which highly conserved, non-flexible, and rigid regions of structural proteins, namely gamma-crystallins, are mutated. Beste *et al.* emphasizes that the mutations were introduced into six hyper variable loops on top of a rigid framework (page 1898, right column, first paragraph, last sentence). This is not equivalent to the positions that the instant claims recite as appropriate for mutation.

Applicants also respectfully note that Beste *et al.* also used a genetic library for constructing their lipocalin mutants. On page 1899, right column, second paragraph, last sentence, Beste *et al.* states that 3.7×10^8 transformants were obtained. Hence, Beste *et al.* also started with billions of transformants and selected the desired lipocalin variants by bringing them into contact with a ligand of choice.

Further, applicants respectfully note that Beste *et al.* identified criteria for mutations including location in a natural ligand-binding pocket, ability to contact a natural ligand, and non-interference with residues from the hydrophobic core. Similar but distinct guidance is offered with respect to the instantly claimed mutants. The claims as amended recite that the mutations are located in two,

three, or four beta-strands of at least one beta-sheet. Additionally, it is recited that the beta-sheet, the beta-strands, and the amino acids located therein must also be located on the surface of the protein. *See also* page 9, third full paragraph, of the instant specification. Thus, and as detailed hereinabove, with respect to gamma-crystallins, there are only 25 candidate amino acids to select from in order to provide the claimed protein.

Continuing, applicants respectfully submit that the Patent Office's remarks regarding the unpredictable consequences of amino acid substitutions on protein function presented on page 7 of the Official Action does not support the instant rejection. The Guo *et al.* reference cited by the Patent Office relates to how amino acid substitutions can destroy a protein's functional activities, in some embodiments presumably by altering the tertiary structure of the protein. Applicants respectfully submit that this is the exact opposite of the instant subject matter, in which alterations of tertiary structure of a polypeptide are encouraged in order to generate new binding activities on otherwise non-binding surfaces.

Furthermore, applicants respectfully reiterate that it is not necessary for one skilled in the art to predict which mutations will yield proteins with the desired binding activity. For example, page 5, first full paragraph; page 9, third paragraph, through page 10, second full paragraph; as well as pages 11 and 12 of the instant specification describe in detail how to obtain the presently claimed proteins without predicting the functional effects of multiple amino acid substitutions and without knowing the relationship between the sequence of a peptide and its tertiary structure. As such, in applying a random mutagenesis method, using a phage display system, and testing the binding activity of resulting mutated proteins towards a binding partner, there is no need to predict any functional effects or structural characteristics. Furthermore, an aspect of the presently claimed subject matter is the mutation of amino acids in well described and well characterized regions of a maximum of, for example, 25 amino acids in gamma-crystallins. Applicants therefore respectfully submit that the instant claims are fully enabled.

Additionally, the appropriate standard for enablement is that the claimed subject matter must be enabled so that a person skilled in the art can make and use the subject matter from the disclosures of the U.S. patent application, coupled with information known in the art, without "undue experimentation". *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). While it *might* require considerable experimentation to arrive at and/or characterize additional mutagenized polypeptides that have acquired the recited binding specificities, the quantity of experimentation to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance". *In re Colianni*, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the U.S. patent application in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed." *In re Wands*, 8 U.S.P.Q.2d at 1404 (*citing In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *U.S. v. Telectonics, Inc.*, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). It is further noted that the level of skill in this art is high. As noted in the *In re Wands* decision, this factor must also be considered in evaluating compliance with 35 U.S.C. §112, first paragraph.

Thus, "an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance". *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). Applicants respectfully submit that the instant specification provides sufficient direction and guidance for one of skill in the art to practice the presently disclosed subject matter using techniques that are either described in the specification or are well known in the art without undue experimentation.

Summarily, applicants respectfully submit that the subject U.S. patent application provides adequate guidance and instruction such that one having

ordinary skill in the art can make and use the present invention as claimed in pending claims 1, 5-11, 16, 26-28, 42, and 46. Indeed, applicants respectfully note that 35 U.S.C. §112, first paragraph, requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate in the scope of the claims, and this requirement has been met. Accordingly, these claims are believed to be in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph. Claims 1, 8, and 46 have been canceled, and thus the instant rejection is believed to be moot as to these claims. As a result, allowance of claims 5-7, 9-11, 15, 16, 26-28, and 42 is respectfully and earnestly solicited.

IV. Response to the Written Description Rejection

Claims 1, 5-11, 16, 26-28, 42, and 46 are rejected under 35 U.S.C. 112, first paragraph, upon the contention that they contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. According to the Patent Office, the claimed genus of mutant proteins selected from those listed in claims 1 and 46 is represented by two mutants of gamma-II-crystallin of SEQ ID No. 22 having seven residue-mutation of residues K3, T5, Y7, C16, E18, S20, and D39 into R3, K5, K7, Y16, S18, N20, and L39. These mutants, having very particular substitutions, are asserted to be not sufficiently representative of the genus of mutants of proteins listed in claim 1.

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, and without acquiescing to the Patent Office's assertions, applicants note that claims 1, 8, and 46 have been canceled, and thus the instant rejection is believed to be moot as to these claims.

Continuing with the rejection as applied to the remaining claims, applicants have convincingly shown that gamma-II-crystallin can be mutagenized

in order to arrive at a protein with binding activity towards a specific binding partner. Applicants have shown that mutagenizing gamma-II-crystallin within two, three, or four beta-strands of at least one beta-sheet of said polypeptide allows for the generation of a protein with a new binding activity towards a binding partner. The instant specification describes several methods of how to obtain the proteins claimed and it exemplifies the genus of proteins by mutants of gamma-II-crystallin.

Considering the high degree of conservation in crystallins during evolution, the skilled artisan would have no difficulties in applying the principles disclosed in the instant specification to other gamma-crystallins. Random mutagenesis applied to a gamma-crystallin within two, three, or four beta-strands of at least one beta sheet would be expected to provide a broad population of mutants from which proteins with specific binding activities towards chosen binding partners can be identified. Having provided the information on one species of gamma-crystallin, applicants respectfully submit that one of ordinary skill in the art can properly reproduce the invention with either the same gamma-crystallin or other gamma-crystallins by mutagenizing a small, restricted number of amino acids. Hence, applicants respectfully submit that the written description requirement of 35 U.S.C. §112, first paragraph, is also met.

Accordingly, claims 1, 5-11, 15, 16, 26-28, 42 and 46 are believed to be in compliance with the written description requirement of 35 U.S.C. §112, first paragraph. Subsequent to the cancellation of claims 1, 8, and 46, allowance of claims 5-7, 9-11, 15, 16, 26-28, and 42 is respectfully and earnestly solicited.

V. Discussion of the New Claim

Claim 47 has been added. Support for new claim 47 can be found in pending claim 46, among other places. Thus, applicants respectfully submit that the new claims include no new subject matter.

Applicants respectfully submit that the remarks presented hereinabove with respect to the rejections as applied to the currently pending claims are equally applicable to the new claims. As a result, applicants respectfully submit

that new claim 47 is in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

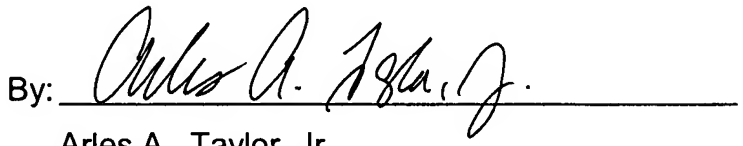
In light of the above amendments and remarks, it is respectfully submitted that claims 5-7, 9-12, 14-16, 26-28, 42, and 47 of the present U.S. patent application are now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiency in payment or credit any overpayment of fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON, TAYLOR, & HUNT, P.A.

Date: August 28, 2007 By: 

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